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EXAMINER	
YANG, NELSON C	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,108	DOSKELAND ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/22/04 1/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

I. Restriction is required under 35 U.S.C. 121 and 372.

1. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

2. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 1-14, drawn to an assay method for determining phosphatase targeting toxins.

Group 2, claim(s) 15-19, drawn to a kit for the detection of phosphatase targeting toxins.

Group 3, claim(s) 20, drawn to the use of the kit for determination of phosphatase-targeting toxins.

3. The inventions listed as Groups 1-3 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. The determination is made based on the contents of the claims as interpreted in light of the description and drawings.

In the instant application, the inventions of groups 1-3 do not form a single general inventive concept, as the special technical feature of the kit of group 2 is known in the art as shown by Johannsson [US 4,668,639] who teaches a kit comprising a first vessel containing a first ligand adapted to bind with a corresponding anti-ligand bound to the surface, and a reagent

solution adapted to bind with the anti-ligand bound with the said first ligand (column 4, lines 55-65), where the anti-ligand can be a phosphatase (column 3, lines 55-65), and the detection of the anti-ligand is performed by measuring the effect of the anti-ligand on a second ligand/anti-ligand interaction. Therefore the inventions do not form a general inventive concept, as they do not share a common special technical feature.

4. During a telephone conversation with Gordan Kit on August 22, 2004, a provisional election was made without traverse to prosecute the invention of group 1, claims 1-14. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

II. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. With respect to claim 1, applicant recites that the immobilized and/or non-immobilized toxin binding ligand is a protein phosphatase enzyme. However, applicant recites that the immobilized ligand is capable of binding to at least one of said toxins, to said non-immobilized ligand or to complexes of said toxin and said non-immobilized ligand, while the non-immobilized ligand is capable of binding to at least one of said immobilized ligand, to said toxins, or to complexes of said toxin and said immobilized ligand, and does not specifically require that either ligand binds to a toxin. Therefore it is unclear whether a protein phosphatase enzyme would be involved if both ligands were capable of binding only to each other. If so, it is unclear what the role protein phosphatase would play. It would also be unclear how the proportion of said immobilized ligand bound by said non-immoblized ligand would be dependent on the toxin content of the sample.

Furthermore, it is unclear whether if both ligands were toxin-binding ligands, whether both would be protein phosphatase enzymes. If so, it is unclear how determining the non-immobilized protein phosphatase enzyme bound to the immobilized protein phosphatase enzyme would aid in determining phosphate targeting toxins. It is unclear if the non-immobilized protein phosphatase enzyme would even be capable of binding to the immobilized protein phosphatase enzyme.

In addition, if both ligands are only capable of binding to complexes of toxins and ligands, it is unclear whether binding would even occur, as the there would be no complexes present for the ligands to bind to, only individual ligands and toxin molecules. Furthermore, if the steps are performed sequentially or separately, it is unclear if there would even be the opportunity for the non-immobilized ligand and toxin to form complexes.

Applicant also recites the limitation that the immobilized ligand is capable of generating directly or indirectly detectable when uncomplexed, when complexed by the toxin, when complexed by a complex of the toxin and the non-immobilized ligand, or when complexed by the non-immobilized ligand or the non-immobilized ligand is capable of generating a directly or indirectly signal when uncomplexed or when complexed. If neither ligands are capable of binding to the toxin and are only capable of binding to each other, it is unclear how generating a detectable signal would aid in the determination of phosphate targeting toxins.

With respect to the limitation that the application of (i) and (ii) to the solid support may be performed separately, sequentially, or simultaneously, it is unclear if performed separately, whether the toxin and non-immobilized ligand would even come in contact with one another, and if so, how this would differ from performing the steps sequentially.

8. With respect to claim 4, applicant recites the limitation that toxin molecules present in the sample compete with the non-immobilized ligand for a limited number of binding sites of the immobilized ligand and any toxin present in the sample is determined relative to the extend of non-immobilized ligand bound or not bound to the binding sites of the immobilized ligand.

If the immobilized ligand is capable of only binding to the non-immobilized ligand, or if the immobilized ligand is only capable of binding to the complex of the non-immobilized ligand and toxin, it is unclear how the non-immobilized ligand would compete with the toxin molecules. Furthermore, it is unclear how the toxin present could be determined relative to the extent of non-immobilized ligand bound or not bound to the binding sites of the immobilized ligand.

If the ligands are both only capable of binding to the toxin, it is unclear how the toxin and non-immobilized ligand would compete for binding spots on the immobilized ligand. Rather, it

would appear that the ligands would compete for the toxin. It also would remain unclear how the toxins would be determined.

Furthermore, if the steps were performed separately, it is unclear how the toxin molecules and non-immobilized ligand would compete for the binding sites of the immobilized ligand.

9. With respect to claim 7, applicant has recited the limitation that the immobilized or non-immobilized ligand is an antibody or antibody fragment. However, applicant has recited in claim 1 that the immobilized and/or non-immobilized toxin binding ligand is a protein phosphatase enzyme. If the ligands are both protein phosphatase enzymes, it is unclear how the ligands could also be antibodies or antibody fragments.

This is also applicable to claims 11-12 with respect to the labeled peptide hepatotoxin or labeled okadaic acid.

10. With respect to claims 9-10, it is unclear why the non-immobilized ligand or immobilized ligand would carry a reporter moiety if the given ligand is capable of generating a detectable signal as recited in claim 1. If applicant is referring to the ligand that is not capable of generating a detectable signal, it is unclear the purpose of providing a reporter moiety to the other ligand, and how the reporter moiety would be utilized in an assay.

11. The remaining claims are indefinite due to their dependence on an indefinite claim.

Claim Rejections - 35 USC § 102

III. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 4, 7, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Usagawa et al [Usagawa et al, Preparation of monoclonal antibodies against okadaic acid prepared from the sponge halichondria okadai, 1989, Toxicon, 27(12), 1323-1330].

With respect to claim 1, Usagawa et al teach a method comprising okadaic acid-bovine serum albumin coated onto the bottom of each well of immunoplate U II, adding 50 μL of a 1:1000 dilution of alkaline phosphatase-F(ab')$_2$ fragment of rabbit anti-mouse IgG+IgA+IgM (H+L) in a washing solution, and then adding okadaic acid to each well of the plate, in order to perform a competitive inhibition ELISA (p.1325, paragraphs 5, 6).

13. With respect to claims 4, 5, 7, the bound okadoic acid-bovine serum albumin and the added okadaic would compete for binding to the alkaline phosphatase-F(ab')$_2$ fragment (p.1325, paragraphs 5, 6).

14. With respect to claim 13, the solid support comprises a microtiter plate (p.1325, paragraphs 5, 6).

15. Claims 1-5, 10, 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Sikorska et al [US 5,264,556].

With respect to claim 1, Sikorska et al teach solid-phase bound antibodies, where the solid support can be plastic or magnetic beads (column 6, lines 35-45). Sikorska et al further teach enzyme labeled anti-mouse IgG anti-serum for use in the assays (column 5, lines 55-67, table 1), indirect detection by a second antibody with a label (column 6, lines 40-47). Sikorska et al teach that the assays involving the bound antibodies, comprise competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG fixed to a solid-phase (column 12,

example II), where free OA inhibits the binding of anti-idiotypic /59 IgG to solid phase bound 6/50 IgG $F(ab')_2$.

16. With respect to claims 2-3, Sikorska et al teach that okadaic acid is produced by several types of marine dino-flagellates and accumulates in marine sponges, mussels and scallops (column 1, lines 10-15).

17. With respect to claims 4-5, Sikorska et al teach assays involving the bound antibodies, such as competition between anti-idiotypic 1/59 IgG and okadaic acid for binding to 6/50 IgG fixed to a solid-phase (column 12, example II), where free OA inhibits the binding of anti-idiotypic /59 IgG to solid phase bound 6/50 IgG $F(ab')_2$.

18. With respect to claim 10, Sikorska et al teach enzyme labeled anti-mouse IgG anti-serum for use in the assays (column 5, lines 55-67).

19. With respect to claim 14, the antibodies are bound to plastic or magnetic beads (column 6, lines 35-45).

Claim Rejections - 35 USC § 103

IV. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1-3, 5, 6, 8, 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holmes [US 5,180,665] in view of Maggio [Maggio, Chapter 3: Enzymes as immunochemical labels, 1980, Enzyme-immunoassay, CRC Press, 54-68].

With respect to claim 1, Holmes teaches a method for quantitatively assaying the presence of DSP toxins such as okadaic acid comprising the steps of preparing a marine extract, fractionating the prepared marine extract and selecting the extract fraction containing the toxin to be assayed, contacting a labeled substrate for protein phosphatase and at least one protein phosphatase to the extract in an assay (column 2, lines 46-61). Holmes does not specify that one of the ligands be immobilized to a solid support.

Maggio, however, teaches that in order to quantitate the amount of analyte present in an enzyme-immunoassay, the extent of reaction of the enzyme-labeled ligand with antibody must be determined, which requires a physical separation of the free and antibody-bound fractions. Maggio further teaches that many of the parameters of a suitable separation technique are shared by bothe enzyme-immunoassays and their analogous radioimmunoassay procedures, and in order to maximize precision and sensitivity, one would like to ensure complete separation of the free and bound fractions, such as by solid phase separation (p. 60-64, part C).

Therefore it would have been obvious in the method of Holmes to have one of the ligands to be bound to a solid support, in order to ensure complete separation of the free and bound labels, so as to maximize the precision and sensitivity of the method.

21. With respect to claim 2, the toxins are accumulated in the midgut glands of bivalves feeding on dinoflagellates (column 1, lines 17-20).

22. With respect to claim 3, the toxins include okadaic acid (column 2, lines 46-50).

23. With respect to claim 5, the presence of toxins such as okadaic acid is quantitatively assayed (column 2, lines 36-50).

24. With respect to claim 6, the samples comprise prepared marine extracts (column 2, lines 50-52).

25. With respect to claim 8, the protein phosphatase can be protein phosphatase 2A (column 4, lines 12-20).

26. With respect to claim 9, the labeled substrate comprises a labeled phosphate group (column 4, lines 25-30).

Conclusion

V. No claims are allowed.

27. The following references are also cited as art of interest: Boland et al [Boland et al, A Unified bioscreen for the detection of diarrhetic shellfish toxins and microcystins in marine and freshwater environments, 1993, Toxicon, 31(11),1393-1405], Simon et al [Simon et al, Highly sensitive assay of okadaic acid using protein phosphatase and paranitrophenyl phosphate, 1994, Natural Toxins, 2, 293-301], Honkanen et al [Honkanen et al, Cyanobacterial nodularin is a potent inhibitor of type 1 and type 2a protein phosphatases, 1991, 40, 577-583], Yochizawa et al [Yochizawa et al, Inhibition of protein phosphatases by microcystis and nodularin associated with hepatoxicity, 1990, Canc Res Clin Onc, 116, 609-614], Honkanen et al [Honkanen et al, Development of a protein phosphatase-based assay for the detection of phosphatase inhibitors in crude whole cell and animal extracts, 1996, Toxicon, 34 (11), 1385-1392], Desmarais et al [US 6,066,715] teach methods of detecting okadaic acid and hepatotoxins.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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